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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,759	04/16/2001	Emilio Barbera-Guillem	B-63	5302

21130 7590 01/26/2005

BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,759	BARBERA-GUILLEM, EMILIO	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 69-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 69-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 14-68 are canceled.

Claims 1-13 have been amended.

Claims 69-115 have been added.

2. Claims 1-13 and 69-115 are pending and under examination. Applciant is reminded that the claims are being examined to the extent that the affinity ligand is a monoclonal antibody specific for CD22 (LL2) (see item no. 4 of the previous Office Action).

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains some New Grounds of Rejections.

Withdrawn Objections And/or Rejections

5. The objection to the specification for containing a segmented line at page 21, line 20 is withdrawn in view of the amendment to the specification.

6. The objection to the Brief Description of the Drawings for not describing the numbered lines in Figure 4 represent is withdrawn in view of Applicant's arguments, which show that the descriptive information requested is found elsewhere in the specification.

7. The rejection of claims 1-5 and 7-12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the amendments to the claims.

Response to Arguments

8. The objection to the first line of the specification for not containing updated priority information is maintained.

The response filed 10/25/2004 updated the priority information with a benefit claim to USSNs 60/103,350 and 60/117,526. It is further noted that USSN 09/411,116 is now U.S. Patent 6,224,866. Applicant is requested update the status of USSN 09/411,116 with its respective U.S. Patent No. (U.S. Patent No. 6,224,866) on the first line of the specification.

Appropriate correction is required.

9. The rejection of claims 6 and 13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 10/25/2004 states that claims 1-13 have been acknowledged as being withdrawn, rendering this rejection moot. It is noted that the previous Office Action, mailed 5/20/2004, stated that claims 1-13 were under examination to the extent that the affinity ligand was a monoclonal antibody that binds CD22 and claims 14-68 were indicated as withdrawn from further consideration. Further, claims 1-13 are indicated as "currently amended" in applicants response and it is noted that claims 6 and 13, not claims 1-13 were rejected under the second paragraph of 35 U.S.C 112. The claims still recite the term "immunotherapeutic composition comprising cobra venom factor", which remains indefinite as it is unclear if cobra venom factor depletes B

cells or is cobra venom factor in addition to another component of the immunotherapeutic composition that depletes B cells (i.e., anti-CD22 antibody).

10. The rejection of claims 6 and 13 and applied to newly added claims 79, 91, 101 and 113 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 10/25/2004 has been carefully considered but is deemed not to be persuasive. The response did not address the rejection as it applies to an immunotherapeutic composition comprising cobra venom factor (claims 6 and 13). Therefore, the rejection is maintained for reasons of record in the previous Office Action. The response also states that the entire specification enables a "vaccine composition". The term "vaccine composition" broadly encompasses preventing cancer. There is no teaching in the prior or post-filing art or in applicant's specification indicating that any cancer can be prevented, thus indicating the high degree of unpredictability of preventing cancer. In fact, vaccine compositions would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancerous cell including preventing genetic mutation, and immortalization. Thus, contrary to applicant's assertion, the instant specification does not enable such a vaccine composition. Further, newly added claims 79, 91, 101 and 113 drawn to compositions comprising a

"vaccine antigen" are not enabled as discussed above and for reasons of record set forth in the previous Office Action mailed 5/20/2004.

11. The rejection of claims 1-2 and 7-10 under 35 U.S.C. 102(b) as being anticipated by Noguchi et al as evidenced by the specification and as evidenced by Trinchieri G is maintained.

The response filed 10/25/2004 has been carefully considered, but is deemed not be persuasive. The response argues that IL-12 should not be interpreted as an effector of B cell depletion in the context of a Th2/Th1 imbalance and the response points out that Trincheri shows that IL-4 is a major cytokine produced during a Th2 response and IL-4 is dominant over that of IL-12 (i.e., Th2 response cytokine) and once a Th1 or Th2 type response is determined early during the immune response, it remains stable, unless major changes take place in the balance of cytokine production during the response. In response to this argument, applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02]. Thus, applicants intended use of the claimed composition for treating a TH2 response and for inducing a cell mediated immune response in an individual having a TH2/TH1 imbalance associated with a pro-tumor immune response is given no patentable weight. Applicants intended use in the context of a TH2/TH1 imbalance has no bearing on what the instantly claimed composition actually is and as such does not distinguish the claimed composition over that of the prior art.

The response further states that IL-12 should not be interpreted as an effector of B cell depletion as treatment of mice with an anti-B cell agent and IL-12 was

significantly less effective in preventing recurrence of tumors than treatment with the anti-B cell agent alone, suggesting that IL-12 reduced, rather than promoted B cell depletion. This argument appears to go more towards enablement of the claimed composition, however, it is noted that Figure 4 and the relevant text at page 40 does not indicate what immunomodulator was actually used and there are many such immunomodulators disclosed at pages 11-12 of the specification. Further, it is noted that during examination the claims are given their broadest reasonable interpretation consistent with the specification. While the claims are read in light of the specification, limitations from the specification are not read into the claims (see MPEP 2111). For purposes of interpreting the claims, the specification at page 8 states that "depletion" in reference to B cells (i.e., B cell depletion) may mean "inhibiting secretion of cytokines or other tumor-promoting soluble factor(s) by activated B cells". As evidenced by Trinchieri, IL-12 is an obligatory factor for TH1 cell generation and proliferation, and as shown in Figure 2, IL-12 inhibits secretion of cytokines from TH2 cells (i.e., humoral/antibody response). For product claims, all that is required is that the prior art teach the substance of the invention. The substance of applicant's invention is a composition comprising (1) an immunotherapeutic composition for effecting B cell depletion; and (2) tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response. Thus, the composition taught by Noguchi et al comprising a nonomer p53 peptide in QS-21 and IL-12 reads on the claims as the nonomer p53 peptide in QS-21 is a tumor-associated antigen that is capable of inducing a cell mediated immune response and IL-12 as evidenced by

Trinchieri inhibits secretion of TH2 cytokines, which in light of the specification is reasonably interpreted as an effector of B cell depletion. If applicant intends the claims to be drawn to a particular embodiment disclosed in the specification, applicant always has the opportunity to amend the claims during prosecution to explicitly recite those limitations to distinguish the claims over the prior art, provided that no new matter is introduced.

12. The rejection of claims 1-5, 7-12 and applied to newly added claims 69-115 under 35 U.S.C. 103(a) as being unpatentable over Apostolopoulos et al in view of Tachibana et al and Parkhouse et al and Wang P. Y-C is maintained.

The response filed 10/25/2004 has been carefully considered, but is deemed not be persuasive. The response states that the specification at pages 21-22 discloses that the instant invention is based on the discovery of a humoral immune response, "a pro-tumor immune response" in individuals bearing solid nonlymphoid tumors and this pro-tumor immune response has the propensity to selectively drive the immune response to comprise a Th2 response, preserve a Th2 response and suppress a cell-mediated immune response (i.e., Th1 response). The response also states that a pro-tumor immune response is a humoral immune response induced by carbohydrate epitopes of shed tumor antigens and in a Th2/Th1 imbalance found in a pro-tumor immune response, the Th2 cytokines inhibit Th1 cell development and suppress a Th1 pattern of cytokine production. In response to these arguments and as discussed above, it is irrelevant that the composition is for treating a Th2/Th1 imbalance in a pro-tumor

immune response as the intended use of a product claim is given no patentable weight (MPEP 2111.02). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., shed tumor antigen) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to a composition comprising (1) an immunotherapeutic composition for effecting B cell depletion or (1) an immunotherapeutic composition comprising a monoclonal antibody that binds CD22 for effecting B cell depletion and (2) a tumor associated antigen capable of inducing a cell mediated immune response comprising a Th1 response and the composition may further comprise (3) an immunomodulator, which is reasonably interpreted as IL-12 in light of the specification at pages 11-12.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Although the response filed 10/25/2004 did not question the merits of the combination of references, the following is reiterated for applicant's convenience. In view of the combined teachings of Apostolopoulos et al and Tachibana et al and Trinchieri G and Parkhouse et al and Wang P. Y-C, it would have been prima facie

obvious at the time the invention was made to modify the teachings of Apostolopoulos et al to produce a composition for inducing a Th1 response, the composition comprising a tumor-associated antigen (i.e., MUC1) and the anti-CD22 antibody-ricin conjugate for depleting normal B cells a taught by Parkhouse et al and to have placed the composition in a solid phase implant as taught by Want P. Y-C to facilitate the delivery of the composition for therapeutic benefit of tumors.

The motivation to make the above modifications comes directly from Apostolopoulos et al who teaches that induction of a humoral immune response (Th2 response/antibody response) gives poor tumor protection accompanied by little cellular immunity and when a cellular immune response (Th1 response) is induced, this results in significant tumor protection, cytotoxic T lymphocytes and little antibody production (i.e., Th2 or humoral response). Additional motivation for the above modifications is made explicit by Tachibana et al who states "immune complexes interfere with cell-mediated immunity to cause enhancement of tumor growth" (see page 458) and "the enhancement of tumor growth was caused by acceleration of humoral response existing beforehand in the tumor-bearing state" (emphasis added) (see page 461). Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have produced a composition comprising an immunotherapeutic composition comprising an anti-CD22 antibody-ricin conjugate, a tumor-associated antigen and optionally further comprise a Th1 promoting immunomodulator such as IL-12 for therapeutic benefit of tumors because Apostolopoulos et al and Tachibana et al teach that a TH2 or antibody response offers poor tumor protection and enhances tumor growth, whereas a Th1

response results in significant tumor protection. Thus, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to combine the anti-CD22 antibody-ricin conjugate to deplete normal B cells to reduce the humoral/antibody immune response with a tumor associated antigen (i.e., MUC1) and further include the immunomodulator, IL-12, which induces a Th1 response (cell mediated immunity) and negatively regulates the Th2 response as taught by Trinchieri G. Furthermore, it would have been prima facie obvious to package the composition in a solid phase implant as taught by Want P. Y-C to facilitate the delivery of the composition and to perform routine optimization to use the immunotherapeutic composition, the tumor-associated antigen and the immunomodulator in combination or separately. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization to administer the components of the composition separately or in combination is not considered inventive, absent objective evidence that separate or co-administration was other than routine, that results from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

New Grounds of Objections/Rejections

13. Claims 5 and 12 are objected to as being drawn to non-elected inventions. Appropriate correction is required.

14. Claims 74-76, 87-89, 97-99 and 109-111 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Claims 74-76, 87-89, 97-99 and 109-111 depend from base claims reciting a composition comprising (a) an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22 for effecting B cell depletion and (b) tumor-associated antigen and optionally further comprising (c) an immunomodulator. Dependent claims 74-76, 87-89, 97-99 and 109-111 recite that the components (i.e., (a)-(c) above) of the composition are each separate components that can be administered individually and as such does not further limit the respective base claims because these separate compositions do not comprise components (a) and (b) and optionally (c) above. The dependent claims (74-76, 87-89, 97-99 and 109-111) do not include every limitation of the respective base claims on which they depend.

15. Claims 70-71, 73, 76, 78, 82-84, 86, 89-90, 93-94, 96, 99-100, 105-106, 108 and 111-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The claims compositions comprising an immunomodulator for inducing a cell mediated immune response comprising a Th1 and the immunotherapeutic composition further comprises an anti-B cell agent for effecting B cell depletion. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. Accordingly, there is insufficient written description encompassing an "immunomodulator for inducing a cell mediated immune response comprising a Th1" and "an anti-B cell agent for effecting B cell depletion" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of an "immunomodulator" and "B-cell agent" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc.

v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin"

fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, an "immunomodulator for inducing a cell mediated immune response comprising a Th1" and "an anti-B cell agent for effecting B cell depletion" does not distinguish any a particular immunomodulator (e.g., IL-12) or anti-B cell agent (e.g., toxins) from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of an "immunomodulator" and the genus of an "anti-B cell agent"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Conclusions

16. No claim is allowed.

17. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827